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ACTION OF THIOL POISONS ON SYNAPTIC TRANSMISSION
OF IMPULSES IN SYMPATHETIC GANGLIA

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Many investigations of the mechanism by which impulses are transmitted from nerve endings to effector cells in various vertebrate animals have disclosed that in a number of divisions of the nervous system the transmission of impulses is connected with the initiation of specific biochemical processes. In regard to nerve fibers of the parasympathetic system and the endings of motor nerves, as well as preganglion fibers of the sympathetic system, it has been shown that the transmission process consists of the synthesis of acetylcholine, the liberation of acetylcholine as a result of the stimulus, and the subsequent decomposition of acetylcholine by enzyme action.

Using specifically acting chemical compounds, Kh. S. Koshtoyants and his co-workers proved that the blocking of sulphydryl groups in the myocardium of frogs by means of ions of heavy metals prevents the negative inotropic action produced by acetylcholine or by an irritation of the vagus (1-3). Substances rich in free sulphydryl groups (e. g., cysteine) counteract this effect by taking up the ions of heavy metals. The significance of the presence of free sulphydryl groups in tissue proteins for the functional condition of the nervous system and for nerve-to-muscle transmission of impulses in frogs has also been demonstrated.

Starting with the above data on the role played by free sulphydryl groups of tissues in producing the sensitivity of tissues to acetylcholine, we attempted to clarify the significance of sulphydryl groups for the transmission of stimuli in synapses of warm-blooded animals.

Our investigation was carried out on the upper cervical sympathetic ganglion of a cat, i. e. a ganglion which has been thoroughly studied as far as the method of investigation is concerned (4) as well as from the standpoint of the mechanism of impulse transmission (5-9). Morphological investigations have shown

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that the upper cervical ganglion has the fundamental structural characteristics of synapses which are typical for higher nervous centers (10-11). A low degree of lability in connection with synaptic transmission in sympathetic ganglia is characteristic for central transmission.

In a number of investigations initiated as a result of A. V. Kibyakov's work (5), liberation of acetylcholine in the ganglion after irritation of the preganglion stem, the stimulating effect of acetylcholine on the ganglion, and the intensive synthesis of acetylcholine by ganglion tissue were observed. It was found that the cholinesterase in ganglion tissue brings about rapid decomposition of the acetylcholine, and that introduction of eserine reinforces the effect due to an irritation of the preganglion stem as well as that due to an addition of acetylcholine to the liquid used for perfusion. It was further established that the quantity of acetylcholine in the ganglion changes, depending on changes in the functional state of transmission. All of these data have led many workers to the conclusion that liberation of acetylcholine is the principal factor of synaptic transmission of impulses.

Recently, Kibyakov, on the basis of work he and his collaborators have done, has denied that liberated acetylcholine plays a leading role in the transmission of impulses through the upper cervical ganglion (6). He now is of the opinion that the active principle which is formed in the ganglion on excitation exhibits a number of characteristics distinguishing it from acetylcholine.

In the present instance, experiments were conducted on cats which had previously received an intraperitoneal injection of urethane (1 g per 1 kg) and of luminal sodium (20 mg per 1 kg). The preparation of the upper cervical sympathetic ganglion was carried out according to a procedure demonstrated by T. V. Pravdich-Neminskiy and a method described by K. M. Bykov (4) and Kibyakov (5, 6). The substance tested was introduced in a Ringer-Lock solution, by means of a syringe, through a rubber tube connected with the arterial cannula. The quantity of liquid used amounted to 0.5-1.0 ml. In experiments in which liberation of acetylcholine by ganglion tissue was determined, the liquid that drained off during the corresponding period of time was collected from the vein cannula. The liquid was then diluted with salt solution until its salt content corresponded to that of the Ringer solution for cold-blooded animals. After this, the liquid was tested for acetylcholine content on the isolated heart of a frog. The fact that the negative inotropic effect produced by the liquid disappeared after atropinization of the heart proved that this effect was actually due to acetylcholine.

Irritation of the preganglion stem was brought about by an induction current with a frequency of 5 pulses per second. The contraction of the third eyelid was recorded by the customary myographic method. By applying control irritations to the postganglion stem, the absence of changes in the functional state of the muscle and of nerve-muscle transmission was checked.

As substances which react with free sulphydryl groups of proteins, mercuric chloride, cadmium chloride, monoiodoacetic acid, and parachloromercuribenzoate were used. The action of mercuric chloride was evident at comparatively high concentrations (1×10^{-4} and higher) and was expressed in an excitation of the ganglion replaced by a gradual and irreversible suppression of synaptic transmission and of reactivity towards acetylcholine. Under these conditions, cysteine did not eliminate the effect due to mercuric chloride. In some cases, cysteine brought about a partial and brief restoration of the original condition. An effect similar to that of mercuric chloride was produced by monoiodoacetic acid, which affected ganglia only in concentrations of 1×10^{-2} . Because of its low solubility, parachloromercuribenzoate could be tested only in concentrations at which it did not produce any noticeable effect on the ganglion.

- 2 -

RESTRICTED

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As distinguished from the three substances mentioned above, cadmium chloride, on introduction into the perfusion liquid, produced a very characteristic effect, consisting in reversible suppression of synaptic transmission. This phenomenon was analyzed in the course of subsequent experiments.

If cadmium chloride is introduced during a prolonged irritation of the preganglion stem, this substance produces a rapid relaxation of the third eyelid. Subsequent addition of cysteine to the perfusion liquid results in a sharp rise of the curve of contraction of the third eyelid, bringing the curve almost to its initial height (See Figure 1 appended). Acetylcholine, when added to the perfusion liquid during a blockade of transmission produced by cadmium chloride, brings about a contraction of the third eyelid which does not differ in any respect from the contraction produced by it before application of the cadmium blocking. This effect is clearly apparent in experiments with a prolonged irritation of the preganglion stem (See Figure 2) as well as experiments in which brief electric irritations alternating with the application of acetylcholine are applied (See Figure 3). It follows from this that cadmium chloride does not change the sensitivity of the ganglion to acetylcholine introduced from the outside, although it inhibits transmission in the ganglion. Transmission was always restored on addition of cysteine, although cysteine as such does not exert any apparent effect on the functions of the ganglion.

Against the background of a blockade of synaptic transmission brought about by cadmium chloride, potassium ions, like acetylcholine, retained a capacity to stimulate the ganglion. Furthermore, the relationships between potassium, acetylcholine, and eserine which existed before the application of cadmium chloride were preserved. Eserine produced a brief restoration of transmission in the ganglion.

In analyzing the reasons for the selective exclusion of synaptic transmission by cadmium chloride with simultaneous retention of the capacity of the ganglion to be directly stimulated by acetylcholine, we decided to check whether the cessation of the effectiveness of preganglionic impulses might not be due to a disturbance of the acetylcholine metabolism and a failure of the evolution of acetylcholine in synapses. With this aim, we determined the extent of liberation of free acetylcholine into the perfusion liquid on application of an electrical irritation to the preganglion stem in the presence or absence of cadmium chloride as well as after restoration of transmission [in the presence of cadmium chloride] by means of cysteine.

It was found in all experiments that acetylcholine, which normally is liberated on stimulation of the nerve and is present in a concentration of 1×10^{-8} in the perfusate, can no longer be detected in the perfusate on preganglionic stimulation if the ganglion has been treated with cadmium chloride.

After treatment with cysteine, liberation of acetylcholine into the perfusion liquid as a result of preganglionic stimulation is restored together with transmission through the ganglion (See Figure 4). It was occasionally observed that when cadmium chloride or cysteine was applied acetylcholine was liberated. The effect was relatively weak in the case of cysteine.

A distinguishing characteristic of the action of cadmium ions is that this action inhibits transmission without reducing the sensitivity of the postganglionic neuron to either acetylcholine or potassium ions.

Determination of the acetylcholine content in the eserinated perfusate drained from the ganglion showed that treatment of the ganglion with cadmium chloride not only stops the transmission of impulses, but also results in cessation of the acetylcholine liberation from this ganglion that is due to irritation of the preganglion stem. The introduction of cysteine, in restoring transmission, also restores the liberation of acetylcholine following stimulation.

- 3 -

RESTRICTED

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The data obtained show the significance of tissue sulfhydryl groups in the process of synaptic transmission of impulses in mammals. They also serve to confirm the significance of acetylcholine metabolism in the transmission of impulses by sympathetic ganglia.

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[Figures follow on next page.]

- 4 -

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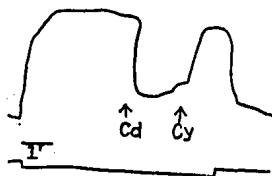
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FIGURE 1. CURVE OF THE CONTRACTION OF THE THIRD EYELID OF A CAT DURING A PROLONGED IRRITATION. THE ARROWS INDICATE INTRODUCTION OF CdCl_2 (IN A CONCENTRATION OF 5×10^{-4}) AND OF CYSTEINE (IN A CONCENTRATION OF 5×10^{-3}).



FIGURE 2. CURVE OF THE CONTRACTION OF THE THIRD EYELID OF A CAT. (1 AND 2): APPLICATION OF ELECTRIC IMPULSES; (2 AND 5): INTRODUCTION OF ACETYLCHOLINE IN A CONCENTRATION OF 5×10^{-4} ; (4): INTRODUCTION OF CdCl_2 IN A CONCENTRATION OF 2×10^{-4} ; (6): INTRODUCTION OF CYSTEINE IN A CONCENTRATION OF 5×10^{-3} .

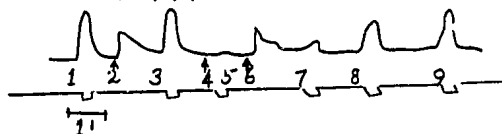


FIGURE 3. CURVE OF THE CONTRACTION OF THE THIRD EYELID OF A CAT. (1,3,5,7,8,9): RESPONSES TO APPLIED ELECTRICAL IMPULSES EQUAL IN STRENGTH; (2 AND 6): RESPONSES TO THE INTRODUCTION OF ACETYLCHOLINE IN A CONCENTRATION OF 5×10^{-4} ; (4): RESPONSE TO THE INTRODUCTION OF CdCl_2 IN A CONCENTRATION OF 2×10^{-4} .

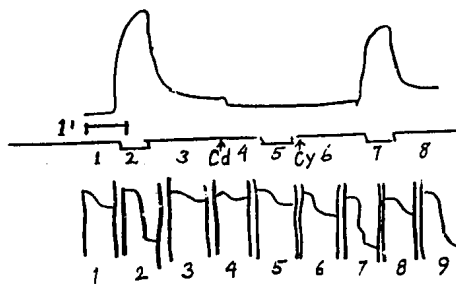


FIGURE 4. UPPER CURVE: CONTRACTION OF THE THIRD EYELID OF A CAT. THE SCALE UNDER THE CURVE INDICATES IRRITATIONS THAT HAVE BEEN APPLIED. THE ARROWS INDICATE INTRODUCTION OF CdCl_2 IN A CONCENTRATION OF 5×10^{-4} AND OF CYSTEINE IN A CONCENTRATION OF 5×10^{-3} . LOWER CURVE: TESTING ON THE ISOLATED HEART OF A FROG OF PERFUSATE TAKEN AT THE MOMENTS WHICH CORRESPOND TO THOSE INDICATED BY THE SAME FIGURES ON THE UPPER CURVE; (9): THE EFFECT OF ACETYLCHOLINE IN A CONCENTRATION OF 1×10^{-8} .

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- 5 -

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